

Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs

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Bioequivalence studies for Locally Acting Drugs

Clinical Endpoint **Bioequivalence** Studies for Locally

Acting Drugs. Dena R. **Hixon**, MD. Associate ...

http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S1_18_Hixon.ppt - Cached -



Systemic Drugs

- ∞ Delivered to the bloodstream for distribution to site(s) of action in the body
- ∞ BE determined with PK studies
 - Relatively short studies
 - Relatively little variability in results
 - Relatively small number of subjects

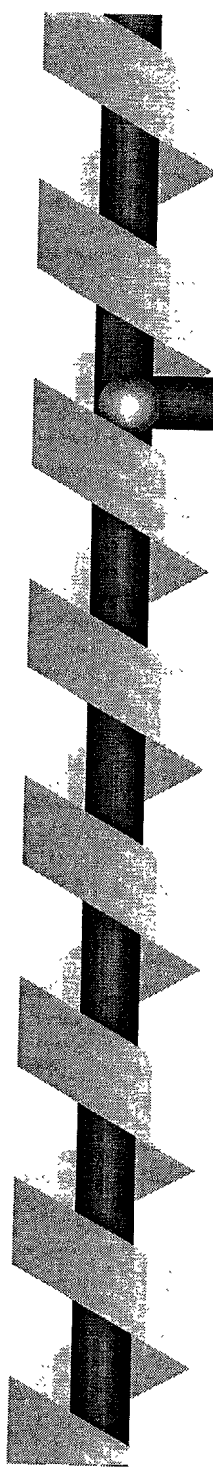


Locally-Acting Drugs

- ⌚ Not intended to be absorbed into the bloodstream
- ⌚ Delivered directly to sites of action in the skin, mouth, eyes, ears, nose, vagina, urinary tract, or gastrointestinal tract

Locally-Acting Drugs

- ∞ Topical acne creams, lotions, or gels
- ∞ Topical or vaginal antifungal creams or suppositories
- ∞ Oral lozenges for oral candidiasis
- ∞ Ophthalmic drops for conjunctivitis
- ∞ Otic drops for external otitis
- ∞ Oral vancomycin for pseudomembranous colitis
- ∞ Nasal sprays for rhinitis
- ∞ Orally inhaled products for asthma



BE of locally-acting drugs

- ∅ PK studies are not adequate
- ∅ Pharmacodynamic (PD) studies for topical steroids
- ∅ Most require clinical endpoint studies
- ∅ Combination products may require both PD and clinical endpoint studies



Clinical endpoint studies

- ∞ 3-arm comparative trials of generic vs. reference listed drug (RLD) vs. placebo
- ∞ Treatment of an approved indication in a patient population according to the labeled dosing of the RLD.
- ∞ Trial design and endpoints similar to NDA



Clinical endpoint studies

- ∞ Both generic and RLD must be statistically superior to placebo ($p < 0.05$) in order to assure that the study is sensitive enough to show a difference between products.
- ∞ Same established BE requirements as for other types of BE studies

Challenges of clinical endpoint studies

- ∩ Clinical endpoints more variable than PK but must meet the established BE limits
- ∩ May require several hundred patients
- ∩ Study duration may be several weeks depending upon the approved labeling
- ∩ Very expensive to conduct
- ∩ May present more safety concerns than PK studies



Challenges of clinical endpoint studies

- ∩ Unknown inter-subject variability within reference population
- ∩ Difficulty in achieving consistency between studies
 - study design
 - study population
 - bioequivalence endpoints
- ∩ Some products require multiple studies

Dermatologic drugs

∂ Antifungals and other anti-infectives

- False negative baseline cultures lead to exclusion of many patients

∂ Acne products

- Multiple endpoints
- Often small effect size and low power to demonstrate BE

∂ Topical acyclovir

- Confusion about indications and endpoints